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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/560,250	06/22/2006	Glen R. Nemerow	5410-007 NATL	5019
7590 LISA A. HAILE, J.D., Ph.D. DLA PIPER US LLP Suite 1100 4365 Executive Drive San Diego, CA 92121-2133			EXAMINER SAJJADI, FEREYDOUN GHOTB	
			ART UNIT 1633	PAPER NUMBER
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b>	<b>Applicant(s)</b>	
	10/560,250	NEMEROW ET AL.	
	<b>Examiner</b>	<b>Art Unit</b>	
	FEREYDOUN G. SAJJADI	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) Responsive to communication(s) filed on 26 February 2008.
- 2a) This action is **FINAL**.                    2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) Claim(s) 1-7, 10-54 and 57-82 is/are pending in the application.
- 4a) Of the above claim(s) 1-7, 10-54, 57, 59-68 and 72-79 is/are withdrawn from consideration.
- 5) Claim(s) \_\_\_\_\_ is/are allowed.
- 6) Claim(s) 58, 69-71 and 80-82 is/are rejected.
- 7) Claim(s) \_\_\_\_\_ is/are objected to.
- 8) Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on \_\_\_\_\_ is/are: a) accepted or b) objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) All    b) Some \* c) None of:
  1. Certified copies of the priority documents have been received.
  2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)            | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)   | Paper No(s)/Mail Date. _____ .                                    |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>2/26/2008</u> .   | 6) <input type="checkbox"/> Other: _____ .                        |

## **DETAILED ACTION**

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

### ***Claim Status***

Applicants' response of February 26, 2008, to the non-final action dated November 28, 2007 has been entered. Claims 1-7, 10-54 and 57-79 are pending in the application. No claims have been cancelled. Claim 58 has been amended, and claims 80-82 newly added. Claims 1-7, 10-54, 57, 59-68 and 72-79 stand withdrawn from further consideration with traverse. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144). See MPEP § 821.01.

Claims 58, 69-71 and 80-82 are under current examination. Applicants should note that the instant claims have been examined commensurate with the scope of the elected invention and the species of the invention. Applicants previously elected SEQ ID NO: 48, corresponding to a modified last repeat, though the sequence was not recited in the examined claims. Applicants have presented SEQ ID NO: 48 in new claim 82. As SEQ ID NO: 48 corresponds to the last repeat of Ad37 (serotype D), examination of new claims 80 and 81 has been limited to Ad37, with the additional Ad species recited in claim 81 representing non-elected species.

### ***Information Disclosure Statement***

The information disclosure statement filed 2/26/2008 is in compliance with 37 CFR 1.98(a)(2). Accordingly the references presented therein have been considered, and indicated as such on Form 1449.

### ***Response to Objections to the Specification/Abstract***

Applicants have correctly noted that an abstract of the disclosure was published with the international application under PCT Article 21, thus a separate abstract is not required. Accordingly, the previous objection is hereby withdrawn.

### ***Response to Failure to Comply with Nucleotide and /or Amino Acid Sequence Disclosures***

Applicants have correctly noted that the consensus sequence depicted in Figure 1B has been indicated as having the sequence set forth in SEQ ID NO: 49, in the brief description of the Figure. Hence, the previous objection is hereby withdrawn.

### ***Response to Claim Objections***

Claim 58 was objected to for reciting non-elected subject matter that include various modifications in the fiber and the third  $\beta$ -repeat of the fiber shaft, in the previous office action dated November 28, 2007. In view of Applicants' amendment of the claim to limit the claim language to that of the elected invention, the previous objection is hereby withdrawn.

### ***Response to Claim Rejections - 35 USC § 102***

Claims 58 and 69 stand rejected under 35 U.S.C. 102(e) as being anticipated by Vigne et al. (U.S. Patent No.: 6,911,199; effective filing date: Aug. 27, 1998). The rejection set forth on pages 4-6 of the office action dated November 28, 2007 is maintained for reasons of record.

The claims as amended encompass an adenovirus particle comprising a fiber shaft protein modified in at least one amino acid in the last full  $\beta$  repeat to reduce CAR binding, and a modification in the fiber knob to further reduce CAR binding.

Vigne et al. teach targeted adenovirus vectors for delivery of heterologous genes, wherein modifications of the internal sites of the adenovirus fiber protein that include short targeting peptides fused to the C-terminus of the fiber protein, or the fiber HI loop (knob) target the modified adenoparticles to specific cell types (Title and Abstract). Specifically disclosing that the fiber protein can be modified to have a fiber shaft that is shorter than a wild-type fiber shaft, in particular by an in-frame deletion or by replacing it with the shaft from another serotype (column 6). In Example 3, Vigne et al. teach a shortened Ad5 shaft that retained only 6 or 9 repeats instead of 22 in the native protein (column 30), and additionally teach using SOE35Kg primer corresponding to the last repeat of the Ad3 fiber shaft and primers that include modifications resulting in the creation of restriction sites to generate an intertypic fiber composed of the Ad5 tail, the Ad3 shaft and part of the Ad5 knob, and flanked with unique restriction sites (columns 31 and 32, bridging). The disclosed mutation thus encompasses a substitution or replacement of the Ad5 shaft with Ad3, comprising a modification in the last full repeat of the fiber shaft. One mutant adenovirus thus generated (vBS1) was noted to bind less efficiently to CAR (column 33). Vigne et al additionally teach that at least a part of the fiber HI loop (knob) is replaced with a ligand peptide or targeting sequence, so as to functionally display its binding specificity at the capsid surface, that may comprise deletion of about 6 to 17 amino acids from the hexon HI loop, preferably not exceeding 11 amino acids (column 4). Further

teaching: "Capsid modifications that impair the native entry pathway (e.g. fibers displaying short shafts) can therefore be combined with capsid modifications that provide an additional, CAR-independent, pathway of infection." (columns 47 and 48; bridging).

Applicants traverse the rejection, arguing that Vigne does not teach or suggest the limitation of instant claim 58, but rather teaches large deletions or substitutions involving all or most of the shaft protein; teaching modified Ad5 fibers in which large portions of the fiber shaft (i.e., repeats 4-16 or repeats 4-19) are deleted, but the native last full repeat is left intact; that Vigne also teaches a substitution of the entire Ad5 fiber shaft with the fiber shaft of Ad3; but is silent with regard to a modification of the last full repeat as required by the present claims.

Applicants' arguments have been fully considered, but are not found persuasive. Applicants are again referred to the teachings of Vigne et al. as outlined above. The language of instant claim 58 is nowhere limiting with respect to the size of the mutation, insertion or replacement, as "at least one amino acid" fails to set an upper limit on mutation size. With respect to modification of the last full repeat, Vigne et al. teach the fiber shaft as comprising pseudorepeats of 15 amino acids, which are believed to form two alternating  $\beta$ -strands and  $\beta$ -bends; and that the overall length of the fiber shaft and the number of repeats varies between different adenoviral serotypes (column 2, lines 22-30). Vigne et al. further teach that the fiber protein can be modified to have a fiber shaft that is shorter than a wild-type fiber shaft, in particular by an in-frame deletion or by replacing it with the shaft from another serotype (column 6). Additionally teaching using SOE35Kg primer corresponding to the last repeat of the Ad3 fiber shaft and primers that include modifications resulting in the creation of restriction sites to generate an intertypic fiber composed of the Ad5 tail, the Ad3 shaft and part of the Ad5 knob, and flanked with unique restriction sites (columns 31 and 32, bridging). The disclosed mutation thus encompasses a substitution or replacement of the Ad5 shaft with Ad3, comprising a modification in the last full repeat of the fiber shaft. Therefore, Vigne et al teach all the limitation of the instant claims, contrary to Applicants' assertion.

The rejection of claims 58 and 69 is thus maintained for reasons of record.

***Response to Claim Rejections - 35 USC § 103***

Claims 58 and 69-70 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Vigne et al. (U.S. Patent No.: 6,455,314; effective filing date: Aug. 27, 1998), in view of Wickham et al. (U.S. Patent No: 2002/0132343; effective filing date Sep. 11, 1998). The rejection set forth on pages 6-7 of the office action dated November 28, 2007 is maintained for reasons of record.

Applicants traverse the rejection, arguing that the references alone or in combination do not teach all of the elements of the present claims and that the references provide no motivation to combine nor would the skilled artisan have had a reasonable expectation of success in achieving an adenovirus particle of the present claims.

Applicants' arguments have been fully considered, but are not found persuasive. Applicants are referred to the response provided above with respect to the teaching of Vigne et al. As previously indicated on the record, Vigne et al. specifically teach additional modification of the fiber knob in the HI loop. Wickham et al. describe adenoviral vectors that contain modifications in the Ad5 fiber knob. Multiple mutations are described as located in the AB loop, CD loop or HI loop (Table 1) that result in reducing CAR native receptor affinity of the resulting mutant particle (column 19; Table 2), thus providing for the deficiency of AB or CD loop in the teachings of Vigne et al., and providing the motivation to introduce mutations in the AB or CD loop. As both Vigne et al. and Wickham et al. are directed to the modification of adenovirus fiber knob, it is unclear why a person of ordinary skill in the art would not be motivated to combine their respective teachings.

Applicants argue that Vigne teaches away from adenovirus particles having the recited fiber shaft modification, because a person of ordinary skill would conclude that CAR binding may be reduced by deletion or replacement of at least repeats 4-16. Such is not found persuasive, because, while CAR binding may be reduced, the binding to other receptors may be enhanced for increased viral entry by inclusion of other targeting moieties or ligands in the fiber knob. In fact, the alteration in CAR binding, or cell tropism is the goal of altered adenoviral targeting. As stated in MPEP 2123, Disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments. *In re Susi*, 440 F.2d 442,

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169 USPQ 423 (CCPA 1971). Furthermore, “[t]he prior art’s mere disclosure of more than one alternative does not constitute a teaching away from any of these alternatives because such disclosure does not criticize, discredit, or otherwise discourage the solution claimed....” *In re Fulton*, 391 F.3d 1195, 1201, 73 USPQ2d 1141, 1146 (Fed. Cir. 2004). As previously indicated, a person of ordinary skill in the art would have been motivated to introduce modifications in either the AB or CD loop of the fiber knob as taught by Wickham et al., because such mutations would provide an additional CAR-independent pathway of infection for adenovirus retargeting.

The rejection of claims 58 and 69-70 is thus maintained for reasons of record.

Claims 58 and 69-71 are rejected under 35 U.S.C. §103(a) as being unpatentable over Vigne et al. (U.S. Patent No.: 6,455,314; effective filing date: Aug. 27, 1998), in view of Hallenbeck et al. (U.S. Patent No: 2002/0137213; effective filing date June 2, 2000).

Applicants traverse the rejection, arguing that the references alone or in combination do not teach all of the elements of the present claims and that the references provide no motivation to combine nor would the skilled artisan have had a reasonable expectation of success in achieving an adenovirus particle of the present claims, because Vigne et al. teaches away from adenovirus particles having the recited fiber shaft modification.

Applicants’ arguments have been fully considered, but are not found persuasive. With regard to the alleged lack of teaching for a fiber shaft modification in the last full β-repeat by Vigne, and the teaching away by Vigne et al. Applicants are referred to the response provided above.

Applicants have further alleged hindsight reconstruction, citing *Interconnect Planning Corp. v. Feil*. Such is not found persuasive, because it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

The rejection of claims 58 and 69-71 is thus maintained for reasons of record.

***New Claim Rejections - 35 USC § 103***

Applicants' claim amendments have necessitated the following new grounds of rejection.

Claims 58 and 80-82 are newly rejected under 35 U.S.C. §103(a) as being unpatentable over Vigne et al. (U.S. Patent No.: 6,455,314; effective filing date: Aug. 27, 1998), in view of Havenga et al. (U.S. Patent Publication No: 2003/0017138; filed Jul. 7, 1999).

The claims as amended encompass an adenovirus particle comprising a fiber shaft protein modified in the last full β-repeat to reduce CAR binding, wherein the modification comprises replacement of the last full β-repeat with a corresponding repeat sequence from an Ad37 serotype D adenovirus, as set forth in SEQ ID NO: 48.

Vigne et al. describe targeted adenovirus vectors for delivery of heterologous genes, wherein modifications of the internal sites of the adenovirus fiber protein that include short targeting peptides fused to the C-terminus of the fiber protein, or the fiber HI loop (knob) target the modified adenoparticles to specific cell types (Title and Abstract). Specifically disclosing that the fiber protein can be modified to have a fiber shaft that is shorter than a wild-type fiber shaft, in particular by an in-frame deletion or by replacing it with the shaft from another serotype (column 6). Additionally disclosing substitution or replacement of the Ad5 shaft with Ad3, comprising a modification in the last full repeat of the fiber shaft (column 33).

While Vigne et al do not specifically describe the serotype D Ad37 virus having the sequence set forth SEQ ID NO: 48, such adenovirus serotype and sequences of the last full repeat of fiber shaft were known in the prior art.

Havenga et al. describe chimeric adenoviruses as vectors, wherein the hybrid adenoviruses contain a genome derived from different adenovirus serotypes, displaying a modified host range that overcome the limitations with currently used serotype C adenoviruses (Abstract). Havenga et al. state: “Preferably, the (chimeric) adenoviruses capable of transducing a CAR negative cell include at least an adenovirus receptor binding part of a fiber protein from an adenovirus of subgroup D” (paragraph [0020], further depicting the fiber shaft sequences of

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type 37 in Fig. 7, and specifically describing Sequence 31, comprising the last full repeat of instantly claimed SEQ ID NO: 48.

Therefore, it would have been *prima facie* obvious for a person of ordinary skill in the art, to combine the teachings of Vigne et al. and Havenga et al. to substitute or modify the last full repeat of the fiber shaft of a serotype 37 in a retargeted adenoviral vector, as instantly claimed, with a reasonable expectation of success, at the time of the instant invention. A person of ordinary skill in the art would have been motivated to introduce a modification in the fiber shaft as taught by both Vigne et al. and Havenga et al., because such mutations would provide an additional CAR-independent pathway of infection for adenovirus retargeting.

### ***Conclusion***

#### **Claims 58, 69-71 and 80-82 are not allowed.**

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. The claims are drawn to the same invention claimed earlier in the application and would have been finally rejected on the grounds and art of record in the next Office Action if they had been entered earlier in the application. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR§1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to FEREYDOUN G. SAJJADI whose telephone number is (571)272-3311. The examiner can normally be reached on 6:30 AM-3:30 PM EST.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Fereydoun G. Sajjadi, Ph.D.  
Examiner, Art Unit 1633

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